The Egyptian Journal of Hospital Medicine (January 2019) Vol. 74 (5), Page 1079-1087

A Case Control Study on the Effect of Vitamin D on Childhood Cancer

Salma B. Galal (1), Somaya M. Lashin (1), Hanaa AbouElyazid (1), Sahar A. Khalil (2) and Doaa S. Ahmed (1)*

1- Department of Community and Occupational Medicine, Faculty of Medicine for Girls, Al-Azhar University.

2-Pediatric Oncology Department, National Cancer Institute, Cairo, Egypt

*** Corresponding author:** Doaa Sadek Ahmed, **E-mail:**doaasadek55@yahoo.com

ABSTRACT

Background: Childhood cancer in Egypt is a growing concern for the society. The role of vitamin D as promising anticancer agent is evident. A limited number of studies have examined vitamin D status among pediatric oncology patients.

Aim of the Work: was to detect some risk factors of childhood cancer, to assess level of vitamin D and identify factors influencing its level in newly diagnosed cancer children and controls.

Subjects and Methods: A case control study was designed including 160 children, aged 1 to 15 years. 80 children were randomly chosen from newly attendants of the National Cancer Institute in Cairo, while controls were recruited from healthy children accompanying parents in a polyclinic in Cairo. The questionnaire included, beside characteristics of parents, risk factors of childhood cancer. A subsample (40 cases, 40 controls) was investigated for serum vitamin D. SPSS 17 was used for statistical analysis.

Results: 63.8% of the diagnosed cancer children were males compared to 55% of controls. Hematological tumor was the most predominant type. Significantly more cases than controls were of higher birth order , had older fathers, less educated mothers, positive family history of cancer, no folic acid supplementation of mothers during pregnancy, and low vitamin D level (p=0.000). In addition, they mentioned less frequent sun exposure days, incorrect timing of exposure, and lack of sport participation.

Conclusion: It is concluded that deficiency of vitamin D, family history of cancer and lack of maternal folic acid were detected as significant risk factors of childhood cancer.

Keywords: Childhood Cancer, Vitamin D.

INTRODUCTION

Childhood cancers describe cancers that occur between birth and 15 years of age. They differ from adult cancers in the way they grow and spread, how they are treated, and how they respond to treatment. Globally, 215,000 cancers are approximately diagnosed per year in that age group with an estimated 80,000 cancer-related annual deaths among them [(1)].It was documented that cancer incidence rates increased in children by 0.6% per year from 1975 to 2012 [(2)].

More than 80% of all childhood cancer cases occurs in low- and middle-income countries. In **Egypt,** it is of concern as its incidence is increasing rapidly. There is a large uncertainty accompanies statistics for cancer incidence and survival. Children's Cancer Hospital estimated 8500 children diagnosed with cancer in Egypt every year [(3)]. Results of the national population-based cancer registry showed a crude incidence rate equal to 128.6 per million children. The rates were 146.6 and 116.0 for males and females respectively. These cancers represented 2.7% of total cancer for all ages [(4)].

The development of cancer is a multistep process which is characterized by uncontrolled cell growth and division. Malignant transformation is a complex process starts by initiation of cellular genetic mutation followed by promotion of initiated cells to become cancerous through environmental substances or even radiation and chemicals (epigenetic changes). Finally cancer can spread to surrounding or distant tissues or organs [(5)].

Through previous studies which mentioned risk factors of cancer, optimal level of vitamin D has been acknowledged as promising anticancer agent through its anti-carcinogenic properties in the form of decreasing cell proliferation, increasing cell differentiation, decreasing angiogenesis, and its

Received: 10/10/2018
Accepted: 29/10/2018

anti-inflammatory effect, therefore, it can prevent cancer metastasis and impede cancer cell growth [6].

Multiple factors are known to influence vitamin D status. Sunshine exposure is the most important factor .Surprisingly sub-optimal levels of vitamin D is notable in the Middle East in spite of its prevailing sunny weather. Moreover, body mass index (BMI), physical activity, and dietary factors are possible factors [7].Nevertheless; vitamin D deficiency and insufficiency are highly prevalent among children worldwide [8].The serum 25-hydroxyvitamin D (25(OH)D) concentration has been accepted as the primary determinant of vitamin D status[9].

The vast majority of research focus on suboptimal levels of vitamin D and increased risk for colon, prostate, ovarian, and breast cancer in adults with limited number of reports on vitamin D status among the Egyptian pediatric oncology population.

STUDY HYPOTHESIS: The null hypothesis was assumed that there is no difference in vitamin D levels between children with newly diagnosed cancer and healthy ones.

THE AIM OF THE CURRENT WORK was to detect some possible risk factors of childhood cancer and to assess level of vitamin D and identify factors influencing its level in children with newly diagnosed cancer in comparison with healthy ones in order to improve prevention, diagnosis and therapy.

SUBJECTSAND METHODS

Study Design: This case control study included a total of 160 participants (80 cases and 80 controls). Cases were taken from newly diagnosed children attending the National Cancer Institute (NCI) in Cairo. Approval of the ethical committee and an oral informed consent from all the subjects was obtained. This study was conducted from January 2016 to December 2017.

Sampling Technique:

- **Type of sample:**

All newly diagnosed cancerous children who attended the outpatient clinic of the NCI were recruited by visiting the clinic two randomly selected days per week.While the control group was apparently healthy children accompany their parents in an non-governmental organization in Cairo who were age and sex matched.

- **Sample size:**

Sample size was calculated by using Power and Sample size program software (PS). We have planned the study of matched sets of cases and controls with 1 matched control per case. If the true odds ratio for cancer in exposed subjects relative to unexposed subjects is 3.3, we had to study 81 case patients with 1 matched control per case to be able to reject the null hypothesis that this odds ratio equals 1 with power of the study0.8.The Type I error probability associated with this test of this null hypothesis is 0.05.

- **Research tools:**

1. A proxy interview questionnaire with parents**:** the structured questionnaire was designed to collect demographic characteristics of the studied children, type of tumor diagnosed, risk factors of childhood cancer, risk factors related to level of vitamin D through sun exposure, dietary intake of vitamin D rich foods, and history of physical activity.
2. Anthropometric measurements:

Body weight and height were measured, then BMI was calculated by percentiles using growth charts with regard to sex for children less than 2 years, while those older than 2years,BMI was calculated by percentiles based on sex and age in months using http://www.cdc.gov/growthcharts/percentile_data_files. BMI percentiles were interpreted according to **CDC (2010)**[10]classification as follow: Underweight (<5th percentiles), normal weight (5th to < 85th percentile), overweight (85th to < 95th percentile), and obese (>95th percentile).

3. Laboratory diagnosis. Subsample of 40 cases and 40 controls was investigated for serum vitamin D using enzyme immunoassay (EIA kit) for the quantitative measurement of total 25 OH vitamin D 2/3 level in serum. Vitamin D status was classified according to the American Academy of Pediatrics (AAP)/LWEPS's and IOM recommendations on cut-off levels for states of vitamin D [11,12] as follow; 25(OH)D < 15 ng/ml was considered deficient, 16-20 ng/ml was considered insufficient while the optimal level was considered >20ng/ml.

- **Statistical analysis:**

Pre-coded data were statistically analyzed using SPSS 17**.** For descriptive purpose, qualitative

data were presented as frequencies and percentages.Mean, standard deviations and ranges were used to describe quantitative numeric variables.To assess the significance in the observed differences between cases and controls, Pearson Chi square- test (X^2) for independence was used for qualitative data and Fishers Exact test was used instead for expected cells less than 5. The Student's independent t-test was used for the differences between means of two continuous variables of unpaired group. The significance level was taken at 0.05 with 95% confidence limit. The results were deemed to be statistically significant if the p value (two tailed) was <0.05. Odds ratios (OR) was calculated. Logistic regression was also used.

RESULTS

The mean age of cases was 7.3 ± 4.3years and that of controls was 7.6± 3.3 years with no statistical significant difference. As regard age group, 36.2 % of cases belonged to age group 1-5 years. Males were more than females among cases than controls (63.8% and 55% respectively)with no significant difference.53.8 % of cases compared to 30 % of controls reside in rural areas, with statistically significant difference. 46.2% of cases had higher birth order (third to seventh child in the family) in comparison with 27.5% in controls with statistically significant difference. In addition; it was found that half (50.0%) of the cases suffered from hematological tumors, 11.2% had brain tumors and 38.8% had different types of solid tumor**. (Fig. 1)**

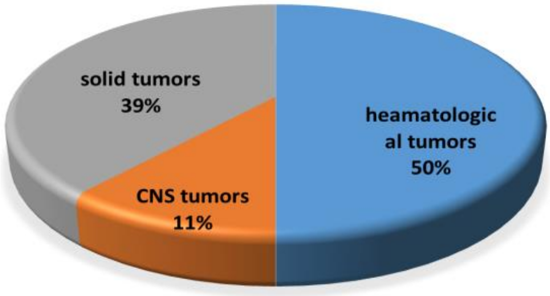

Figure (1): Childhood cancer classification of the studied children.

Table (1): Family profile of the studied children:

Studied groups / Characteristic items	Cases N =80	Cases %	Control N = 80	Control %	Significance tests	P Value
Age of father at child birth (years): (Mean ± SD) Range (minimum-maximum)	**35.4 ± 8.1** (21-64)		**32.2 ± 6.4** (20-50)		t =2.76	**0.006***
Age of mother at child birth (years): (Mean ± SD) Range (minimum-maximum)years	**27.7 ± 6.2** (17-45)		**26.3 ± 5.7** (16-41)		t = 1.57	0.12
Level of father education:					X² = 6.76	0.149
Illiterate	12	15	15	18.8		
Read and write	7	8.8	11	13.7		
Primary& preparatory	5	6.2	7	8.7		
Secondary	41	51.2	25	31.3		
High & postgraduate	15	**18.8**	22	**27.5**		
Level of mother education:					Fischer's Exact =11.02	Exact sig. = **0.024***
Illiterate	27	33.7	19	23.7		
Read and write	4	5.0	10	12.5		
Primary& preparatory	4	5.0	7	8.7		
Secondary	35	43.8	23	28.8		
High & postgraduate	10	**12.5**	21	**26.3**		
Economic status of the family:					Fischer's Exact =3.79	Exact sig. = 0.275
In debt	1	1.2	2	2.5		
Offer routine living requirements	25	31.2	15	18.7		
Offer routine requirements and able to pay in emergency	41	**51.3**	50	**62.5**		
Saving money	13	**16.3**	13	**16.3**		

* Statistically significant difference

Table (1) shows no statistical significant difference between cases and controls as regards mothers' age, fathers' education, and economic status of the family. However, there is significant difference between both groups as regards fathers' age and mother' education.

Table (2): Risk factors of childhood cancer:

Risk factors of childhood cancer \ Studied groups	Cases N=80	%	Control N=80	%	Significance Test	P-value
Family history of cancer:					$X^2 = 15.17$	
○ Yes	33	**41.3**	11	**13.8**	OR = 4.4	**0.000***
○ No	47	58.7	69	86.2	CI= 2.03-9.57	
History of recurrent infection of child since birth:					$X^2 = 14.34$	
○ Yes	28	**35.0**	8	**10.0**	OR= 4.85	**0.000***
○ No	52	65.0	72	90.0	CI=2.05-11.49	
History of child exposure to pesticides (indoors and outdoors):					$X^2 = 8.9$	
○ Yes	13	**16.2**	2	**2.5**	OR= 7.57	Exact sig.=**0.005***
○ No	67	83.8	78	97.5	CI=1.65-34.74	

*Statistically significant difference

Table (2) represents risk factors of childhood cancer among the studied groups. Significantly more cases than controls had family history of cancer, reported history of pesticide exposure, and recurrent infection since birth.

Table (3): Parental Risk factors of childhood cancer:

Parental risk factors \ Studied groups	Cases N =80	%	Control N = 80	%	Significance tests	P Value
Father smoking:**					Fischer's Exact =0.54	Exact sig.= 0.86
○ Ever smoking	38	**47.5**	33	**41.2**		
○ Before conception	3	3.7	5	6.3		
○ After birth	0	0.0	4	5.0		
○ Never	39	48.8	38	47.5		
Number of cigarette smoked/day:	**N=41**		**N=42**		t= 3.53	**0.001***
○ Mean ± SD	22.4 ± 11.6		14.8 ±7.7			
Place of smoking:					$X^2 = 11.5$ OR=5.3 CI=1.94-14.7	**0.003***
○ Indoors/or both indoors and outdoors	34	**82.9**	20	**47.6**		
○ Outdoors	7	17.1	22	52.4		
Pesticides exposure among parents around conception: ○ Yes	18	**22.5**	7	**8.8**	$X^2 = 5.74$ OR= 3.03 CI=1.19- 7.72	**0.017***
○ No	62	77.5	73	91.2		
Folic acid supplementation of mothers during pregnancy: ○ No	63	**78.8**	21	**26.2**	$X^2 = 44.2$ OR=10.4 CI= 5.01-21.63	**0.000***
○ Yes	17	21.2	59	73.8		
Duration of using cell phones (minutes /day): Median - (25-57% interquartile)	30 - (20 -37.5)		20 - (10- 30)		Mann Whitney z =4.63	**0.000***

Table (3) represents parental risk factors of childhood cancer among the studied groups. It was found that 47.5% of cases' fathers were ever smokers compared to 41.2% of controls'. Among those who were smokers; the mean number of cigarette smoked per day was statistically significant higher among cases than their controls, smoking indoors or both indoors and outdoors was statistically significant more frequent among fathers of cases vs. controls. In addition, significantly more parents of cases were exposed to pesticides than controls, and more mothers reported less folic acid supplementation during pregnancy, and longer duration of cellphone use.

Table (4): Serum level of vitamin D among the subsample:

Vitamin D level \ Studied groups	Cases N =40	Control N = 40	Significance Test	P-Value

	N	%	N	%		
○ Deficient (5-15 ng/ml)	11	27.5	0	0.0	Fisher's Exact=18.34 OR=8.3 CI=2.9-23	Exact sig.= **0.000***
○ Insufficient (16-20 ng/ml)	21	52.5	13	32.5		
○ Optimal (21-100 ng/ml)	8	**20.0**	27	**67.5**		

*Statistically Significant difference

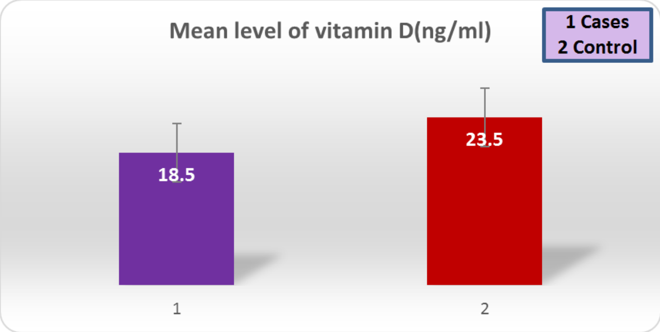

Figure (2): Mean level of vitamin D among cases and controls (t=5.46, P=0.000).

Table (4) and Figure (2) illustrate vitamin D level among cases and controls; the mean level among cases was statistically significant less than that of controls**.** Optimal level of vitamin D was recorded among one fifth of cases in comparison to more than two thirds of controls with statistically significant difference.

Table (5): Logistic regression for predictors of risk factors of childhood cancer:

Predictors	β	Wald	Sig.	OR	95% C.I. for OR	
					Lower	Upper
Child sex (male)	1.193	1.428	0.232	3.297	0.466	23.335
Rural Residence	0.773	.533	0.465	2.167	0.272	17.279
No education of Mothers'	0.520	3.614	0.057	.595	0.348	1.016
Consanguinity	0.745	.602	0.438	2.106	0.321	13.804
History of family cancer	3.237	5.090	0.024	25.469	1.529	424.126
No folic acid supplements of mothers during pregnancy	2.732	6.313	0.012	15.370	1.824	129.529
Frequency of sun exposure	2.179	2.680	0.102	8.834	0.651	119.920
Timing of sun exposure	2.578	5.980	0.014	13.175	1.668	104.054
Level of vitamin D	0.391	8.456	0.004	1.478	1.136	1.923
Sport participation	2.756	3.714	0.054	15.741	0.954	259.703
Constant	-31.205	12.880	0.000	.000		

Table (5) indicate that the logistic regression analysis of the most relevant factors to child cancer were family history of cancer, no folic acid supplements of mothers during pregnancy, lack of sport participation, inappropriate timing of sun exposure, lower frequency of sun exposure, lower level of vitamin D as well as being male, living in rural area and parents' consanguinity with less educated mothers.

DISCUSSION

Although no statistical significant difference was found between cases and controls as regards age, sex, yet significantly more cases are from rural areas than controls,

being exposed to agricultural pesticides. A population‑based study done by ***Gómez‑Barroso et al***.[13]and showed that an excess of risk of childhood cancer among children living in the proximity of crops. The current study revealed that significantly more cases are from higher birth order than controls. Previous studies' findings regarding birth order were controversial, in agreement with our results, ***Hassanzadeh et al.***[14]found an association between increased birth order (≥3) and risk of childhood leukemia among Iranian children. Probably there is an increased exposure to infectious agents in bigger families.

The current study revealed that fathers of cases were statistically significant older than those of controls'. These findings are in accordance with a study done by ***Wang et al.***[15] in California who revealed that children in age groups 0-14 years with older fathers are at increased risk for cancer. In addition, our results revealed that less educated mothers of cases were statistically significant more than those of controls. These findings are in line with a study done by ***Kumar et al.***[16]including 132 children diagnosed with leukemia which found a significant association of lower educated mothers with increased risk of leukemia.

Family history of cancer in our study is significantly more in cases than controls. These findings are in agreement with a study carried out by ***Del Risco Kollerud et al.*** [17] who reported that there was an association between risk of childhood tumors and first-degree family history of early onset of solid tumors which was observed for CNS tumors (2.3-fold), neuroblastoma (2.3-fold), retinoblastoma (6.1-fold), hepatic tumors (4.0-fold), and melanomas (8.3-fold).

The current study revealed that more cases had history of recurrent infection since birth compared to controls with statistically significant difference. These results are similar to ***Maia and Wunsch***[18] in which the association between childhood infection in the first two years of life and leukemia was found. Our finding also showed that significantly more cases had history of pesticide exposure indoors or outdoors than controls. This finding is in accordance with a meta-analysis done by ***Chen et al.***[19] that revealed childhood exposure to indoor but not outdoor residential insecticides was associated with a significant increase in risk of childhood leukemia and lymphomas and there is a positive but not statistically significant association between home pesticide exposure during childhood and brain tumor.

By interpretation of the results regarding smoking of fathers, ***Liu et al.***[20]performed a meta-analysis showed a positive dose-response relationship between childhood ALL and paternal smoking (OR was 1.17, 1.25 and 1.3) for paternal smoking of <10, 10–19, and ≥20 CPD (cigarette per day) respectively. Another meta-analysis done by ***Lee et al.***[21] reported there is an association between paternal smoking at home and all types of leukemias (OR = 1.8) and particularly for ALL (OR was 2.0).

A large international collaborating study done by ***Metayeret al.*** [22] including 47000 children with acute leukemia and 11 000 controls found reduction in risk of leukemia following maternal intake of folic acid supplements during pregnancy. Similarly, our study revealed the decreased folic acid intake in cases during the first trimester than controls.

Our results indicate high prevalence of vitamin D deficiency among cancerous children in comparison with controls. By comparing these findings with the prevalence reported from ***Mohan et al.*** [23] who measured vitamin D concentration in 51 newly diagnosed children with malignancy during their admission over a span of 5 months in India and revealed that half of them had insufficient vitamin D with a much lower mean compared to controls.

Among predictors of childhood cancer in the regression model is parent consanguinity in which it is in agreement with a study comprised 117 patients with ALL and lymphoma and the consanguinity rate was compared with the rate in the general population and concluded that among ALL cases, 80% of families were consanguineous ***Bener et al.***[24]

Furthermore, less frequency and incorrect timing of sun exposure away from midday (10AM-3PM) were detected as predictors of childhood cancer, these results are similar to an Egyptian cross-sectional study done by ***Abo Shady et al.***[25] among a sample of school children aged 9 to 11 years and found that vitamin D level was significantly positively

correlated with frequency sun exposure per week. also, ***Alshahrani et al.*** **[26]**study which was done in Saudi Arabia and found that production of previtamin D3 was observed to occur mostly between 8:00 AM to 4:00 PM with peak hours between 10:00 AM to 12:00 PM.

In addition, participation in sport is a determinant of physical activity and detected as one of the predictors. Similarly ***Almehmadi et al.*****[27]**who concluded that the lowest vitamin D level (25.70 nmol/L) was observed among children who exercised once per week while the highest level (28.10 nmol/L) was observed among those who exercised >3 times per week.

CONCLUSION

Cases of childhood cancer have higher birth order, family history of cancer, older fathers, and less educated mothers than controls. Parents consanguinity, number and place of smoking of fathers, parental pesticide exposure around conception, maternal non-supplementation of folic acid during pregnancy were more among cases than controls .In addition, more cancerous children had history of recurrent infections since birth and/or pesticide exposure either indoor or outdoor. The mean level of vitamin D was significantly lower in cases than controls. It was found that cancerous children were less frequent exposed to sun and mainly exposed through inappropriate timing with lack of sport participation.

LIMITATIONS

Some parents of children with cancer did not show much cooperation to answer the questionnaire due to their feeling of hopelessness. It was difficult to convince the parents of the control group to take a blood sample.

REFERENCES

1. **World Health Organization (2018):** International childhood cancer day: Much remains to be done to fight childhood cancer. www.internationalchildhoodcancerday.org/
2. **Hudson MM, Meyer WH, Pui CH (2015):** Progress born from a legacy of collaboration. J ClinOncol.,33:2935-2937.
3. **Children's Cancer Hospital (2013):** http://beta.57357.com/category/research/
4. **Ibrahim AS, Mikhail NNH, Khaled H (2018):** Current and future incidence of childhood cancer in Egypt: results of the national population-based cancer registry. J Cancer PrevCurr Res. ,9(6):316–321.
5. **Hanahan D , WeinbergRA (2011):** Hallmarks of cancer: the next generation. Cell,144(5):646 - 74.
6. **Krishnan AV, Trump DL, Johnson CS and Feldman D (2010):** The role of vitamin D in cancer prevention and treatment. Endocrinology and metabolism clinics of North America, 39(2): 401-18.
7. **Abu S, Youssef MM, Shehata MA, Salah E and ElMalt HA (2015):** "Association of serum 25-hydroxyvitamin D with life style and dietary factors in Egyptian prepubescent children," Open Access Macedonian Journal of Medical Sciences, 3(1): 80–84.
8. **Juonala M, Voipio A, Pahkala K, Viikari JSA, Mikkila V, Kahonen M (2015):** Childhood 25-OH vitamin D levels and carotid intima-media thickness in adulthood: The cardiovascular risk in young finns study. J. Clin. Endocrinol. Metab.,100:1469–1476.
9. **Bassil D, Rahme M, Hoteit M and Fuleihan G (2013):** Hypovitaminosis D in the Middle East and North Africa Prevalence, risk factors and impact on outcomes. Dermato-Endocrinology, 5(2): 274–298.
10. **Grummer-Strawn LM, Reinold C, Krebs NF (2010):**Use of the World Health Organization and CDC growth charts for children aged 0-59 months in the United States. Recommendations and Reports. MMWR Recomm Rep., 59(RR-9);1-15.
11. **Misra M, Pacaud D, Petryk A *et al*. (2008):** Vitamin D deficiency in children and its management: review of current knowledge and

recommendations.*Pediatrics,* 122(2):398–417.

12. **Ross AC, Taylor CL, Yaktine AL, Del Valle HB(2013):** Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: The National Academies Press; eds. Institute of Medicine of the National Academies.

13. **Gómez‑Barroso, D, García‑Pérez1, J, López‑Abente, G, Tamayo‑Uria, I, Morales‑Piga A *et al*. (2016):** Agricultural crop exposure and risk of childhood cancer: new findings from a case– control study in Spain .Int J Health Geogr., 15: 18.

14. **Hassanzadeh J, Mohammadi R, Rajaeefard AR *et al*. (2011):** Maternal and prenatal risk factors for childhood leukemia in southern of iran. Iran Red Crescent Med J., 13: 398-403.

15. **Wang R, Metayer C, Morimoto L, Wiemels JL, Yang J, DeWan AT, Kang A,Ma X(2017):**Parental Age and Risk of Pediatric Cancer in the Offspring: A Population-Based Record-Linkage Study in California. Am J Epidemiol.,186(7): 843-856.

16. **Kumar A, Vashist M, Rathee R (2014)**: Maternal Factors and Risk of Childhood Leukemia.Asian Pac J Cancer Prev., 15(2): 781-784.

17. **Del RiscoKollerud R, Gerhard Blaasaas K, Claussen B, Nafstad P, Cannon-Albright LA, Ruud E, Næss O (2018):** Family history of cancer and the risk of childhood solid tumours: A Norwegian nationwide register-based cohort study. British Journal of Cancer, 118(6): 905-912.

18. **Maia RD, WunschFilho V (2013):** Infection and childhood leukemia: review of evidence. Revista de saudepublica.,47:1172-85.

19. **Chen M, Chang CH, Tao L, Lu CH (2015):** Residential Exposure to Pesticide During Childhood and Childhood Cancers: A Meta-Analysis. Pediatrics, 136 (4): 719-729.

20. **Liu R, Zhang L, McHale CM, Hammond SK (2011):**Paternal smoking and risk of childhood acute lymphoblastic leukemia: systematic review and meta-analysis. Journal of oncology, 85:4584.

21. **Lee KM, Ward MH, Han S, Ahn HS, Kang HJ, Choi HS, Shin HY *et al*. (2008):** Paternal smoking, genetic polymorphisms in CYP1A1 and childhood leukemia risk. Leukemia research, 33(2): 250-8.

22. **Metayer C, Milne E, Dockerty JD, Clavel J, Pombo-de-Oliveira MS, Wesseling C, Spector LG, Schuz J *et al*. (2014):**Maternal supplementation with folic acid and other vitamins and risk of leukemia in offspring: a Childhood Leukemia International Consortium study. Epidemiology, 25(6): 811–822.

23. **Mohan R, Mohan G, Scott JX, Rajendran A, Paramasivam V and Ravindran M(2016):** Vitamin D insufficiency among children with cancer in India. Indian journal of medical and paediatric oncology: official journal of Indian Society of Medical &Paediatric Oncology, 37(1), 14-9.

24. **Bener A, Denic S and Al-Mazrouei M (2001):** Consanguinity and family history of cancer in children with leukemia and lymphomas. Cancer, 92, 1–6.

25. **Abu Shady MM,Youssef MM, Salah El-Din EM, AbdelSamie OM, Megahed HS, Salem SM *et al*.(2016):**Predictors of Serum 25-Hydroxyvitamin D Concentrations among a Sample of Egyptian Schoolchildren. The Scientific World Journal, 2016:8175768.

26. **Alshahrani FM, Almalki MH, Aljohani N, Alzahrani A, Alsaleh Y and Holick MF (2013):** Vitamin D: Light side and best time of sunshine in Riyadh, Saudi Arabia. Dermato-Endocrinology, 5(1): 177-80.

27. **Almehmadi BM, Fallata EM, Alqahtani SZ *et al*. (2016):** The Effects of Physical Activity and Sun Exposure on Vitamin D Status among Children from Jeddah, Saudi Arabia. J Pediatr Care, 2: 1.